Amendments to the Specification

Please amend the title of the application as follows:

[[ARP]] ACETYLCHOLINESTERASE (ACHE)-DERIVED PEPTIDE AS AN INDUCER OF GRANULOCYTOPOIESIS, USES AND METHODS THEREOF

Please replace paragraph **[0020]** of the published application with the following rewritten paragraph:

[0020] In this view, in a first aspect, the present invention provides the use of an AChE-derived peptide, ARP_{26}, and any functional fragments thereof, as an agent for the induction of the production of granulocytes, or for the enrichment of the granulocytic cell population, wherein said peptide is denoted by ~~SEQ. ID. NO.1~~ SEQ ID NO:1. The peptide used by the invention comprises the following amino acid sequence:

N'-GMQGPAGSGWEEGSGSPPGVTPLFSP-C'

Please replace paragraph **[0022]** of the published application with the following rewritten paragraph:

[0022] In another aspect, the present invention comprises the use of an AChE-derived peptide as an agent for ~~ex vivo or in vitro~~ *ex vivo* or *in vitro* manipulation of cells to induce granulocyte cell differentiation, wherein said peptide is denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1.

Please replace paragraph **[0023]** of the published application with the following rewritten paragraph:

[0023] The AChE-derived peptide denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1, or any functional fragments thereof, are also to be used as an agent for pre-transplant priming of hematopoietic stem cells.

Please replace paragraph **[0025]** of the published application with the following rewritten paragraph:

[0025] In a further aspect, the present invention provides the use of an AChE-derived peptide, or any functional fragments thereof, in the preparation of a pharmaceutical composition for the treatment and/or prevention of conditions that trigger low granulocyte count, wherein said peptide is denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1. Said composition may also be used in pre-transplant priming of ~~hematopoletic~~ hematopoietic stem cells. Such conditions may be, for example, leucopemia, acute myeloid leukemia (AML), and particularly neutropenia.

Please replace paragraph **[0026]** of the published application with the following rewritten paragraph:

[0026] In an even further aspect, the present invention provides a method of treatment of conditions that induce leucopenia, comprising the steps of administrating a therapeutically-effective amount of an AChE-derived peptide or a composition thereof to a subject in need, wherein said AChE-derived peptide is denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1.

Please replace paragraph **[0027]** of the published application with the following rewritten paragraph:

[0027] The invention also refers to an ~~in vivo~~ *in vivo* method for the prevention and/or treatment of conditions wherein lymphocyte activity is reduced, such as chronic stress, autoimmune diseases, inflammation, rheumatoid arthritis, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), fibromyalgia, multiple chemical sensitivity, post-irradiation, chemotherapy in a subject in need, comprising administering a ~~therapeutically effective~~ therapeutically-effective amount of an AChE-derived peptide, or any functional fragments thereof, to an individual suffering or prone to said conditions, wherein said peptide is denoted by ~~SEQ. ID. NO.1~~ SEQ ID NO:1.

Please replace paragraph **[0029]** of the published application with the following rewritten paragraph:

[0029] The invention provides an ~~ex vivo or in vitro~~ *ex vivo* or *in vitro* method of prevention and/or treatment of conditions wherein lymphocyte activity is reduced, such as chronic stress, autoimmune diseases, inflammation, rheumatoid arthritis, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), fibromyalgia, multiple chemical sensitivity, post-irradiation, chemotherapy in a subject in need, comprising obtaining blood from said subject, isolating immature cells and contacting said cells with an AChE-derived peptide, or any functional fragments thereof, wherein said peptide is denoted by ~~SEQ. ID. NO.1~~ SEQ ID NO:1.

Please replace paragraph **[0030]** of the published application with the following rewritten paragraph:

[0030] In addition, a method of priming of hematopoietic stem cells pre-transplant is presented, comprising obtaining said cells, isolating from said cells [[a]] an immature, CD34+ rich population, and exposing said cell population to an AChE-derived peptide, its functional fragments or derivatives, or compositions comprising thereof, wherein said peptide is denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1. Most importantly, said cells may be obtained from the subject in need of said transplant or from another donor.

Please replace paragraph **[0031]** of the published application with the following rewritten paragraph:

[0031] Lastly, the invention also provides a method of inducing adult blood cells to produce cytokines, comprising obtaining said cells from a subject in need of cytokine-producing blood cells, isolating immature cells and contacting said cells with an AChE-derived peptide, wherein said peptide is denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1. This method is particularly advantageous for patients with neutropenia.

Please replace paragraph **[0033]** of the published application with the following rewritten paragraph:

[0033] FIG. **1**A: C-terminal amino acid sequence unique to the human AChE-S variant; SEQ ID NO:2.

Please replace paragraph **[0034]** of the published application with the following rewritten paragraph:

[0034] FIG. **1**B: C-terminal amino acid sequence unique to the human AChE-R variant; SEQ ID NO:1 ([[the]] The sequences in A and B share a similar core domain. Note that ASP, but not ARP, includes a C-terminal cysteine residue (asterisk) that enables AchE-S multimerization).

Please replace paragraph **[0141]** of the published application with the following rewritten paragraph:

[0141] The peptide used by the invention comprises the following amino acid sequence:

(~~SEQ. ID. NO. 1~~ SEQ ID NO:1)
N'-GMQGPAGSGWEEGSGSPPGVTPLFSP-C' .

Please replace paragraph **[0153]** of the published application with the following rewritten paragraph:

[0153] The dose-dependent pattern of this effect further indicates that either too high or too low concentrations of ARP_{26} fail to induce AChE-R mRNA accumulation, suggesting strict dependence of the splice shift process on previously produced AChE-R amounts which, in turn, reflects splicing regulation of the pre-AChE mRNA transcript in hematopoietic cells. ASP_{40}, [[The]] the C-terminal peptide of AChE-S (denoted by ~~SEQ. ID. NO. 2~~ SEQ ID NO:2), failed to induce such effects (FIG. **11**D-**11**E), supporting the specificity of the effect of ARP on prolonged granulocytosis. Vis-à-Vis the results obtained in Example 12, ARP may be used to treat hematopoietic stem cells ~~ex vivo~~ *ex vivo*, driving the cells to the granulocytic differentiation pathway.

Please replace paragraph **[0171]** of the published application with the following rewritten paragraph:

[0171] In a further aspect, the present invention provides the use of an AChE-derived peptide or its functional fragments or derivatives, in the preparation of a pharmaceutical composition for any one of the treatment and/or prevention of conditions that trigger low granulocyte count, such as leucopenia, and particularly neutropenia, and in pre-transplant priming of hematopoietic stem cells, wherein said peptide is denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1.

Please replace paragraph **[0174]** of the published application with the following rewritten paragraph:

[0174] In an even further aspect, the present invention provides a method of treatment of conditions that induce leucopenia, comprising the steps of administrating a ~~therapeutically effective~~ therapeutically-effective amount of an AChE-derived peptide or a composition thereof to a subject in need, wherein said AChE-derived peptide is denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1. Leucopenia includes any condition in which the number of white blood cells is reduced. One particular condition is neutropenia.

Please replace paragraph **[0176]** of the published application with the following rewritten paragraph:

[0176] Thus, the invention also refers to an ~~in vivo~~ *in vivo* method for the prevention and/or treatment of conditions wherein lymphocyte activity is reduced, such as chronic stress,

autoimmune diseases, inflammation, rheumatoid arthritis, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), fibromyalgia, multiple chemical sensitivity, post-irradiation, chemotherapy in a subject in need, comprising administering a ~~therapeutically effective~~ therapeutically-effective amount of an AChE-derived peptide, its functional fragments or derivatives, or compositions comprising thereof, to an individual suffering from or prone to said conditions, wherein said peptide is denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1.

Please replace paragraph **[0185]** of the published application with the following rewritten paragraph:

[0185] Lastly, the invention also provides an ~~ex vivo~~ *ex vivo* method of inducing adult blood cells to produce cytokines, comprising obtaining said cells from a subject in need of cytokine-producing blood cells, isolating immature cells and contacting said cells with an AChE-derived peptide, wherein said peptide is denoted by ~~SEQ. ID. NO. 1~~ SEQ ID NO:1.

Please replace paragraph **[0215]** of the published application with the following rewritten paragraph:

[0215] Experiments with real-time quantitative PCR were performed with the Lightcycler™ system (Roche, Switzerland) and SYBR Green PCR Master Mix (Applied Biosystems). Primers for Ikarosl and mCtBP were designed using the Lightcycler™ sequence-detection software (Roche, Switzerland). Primer sequences for mFOG, mGATA1, Runx 1/AML1, PU1, β-globin, STAT5, and the housekeeping gene β actin (SEQ ID NOS:3-14), as well as amplification conditions, are listed in Table 1. Purity of the PCR products was verified by a melting curve analysis using the Lightcycler™ system, and by agarose gel analysis.

Please replace Table 1 as originally filed with the following replacement Table 1:

Table 1: Primer sequences used for Real Time PCR

Primer	Sequence	Annealing Temperature
GATA1 + (SEQ ID NO:3) GATA1- (SEQ ID NO:4)	5'-3' TCTTCTCTCCCACTGGGAGCCCT 5'-3' CTTCTTGGGCCGGATGAGAGGCC	65ºC
LMO2 + (SEQ ID NO:5) LMO2 – (SEQ ID NO:6)	5'-3' TGGATGAGGTGCTGCAGATA 5'-3' CCCATTGATCTTGGTCCACT	65ºC
RUNX1/AML1 + (SEQ ID NO:7) RUNX1/AML1 – (SEQ ID NO:8)	5'-3' ACTTCCTCTGCTCCGTGCTA 5'-3' GTCCACTGTGATTTTGATGGC	65ºC
PU.1 + (SEQ ID NO:9) PU.1 - (SEQ ID NO:10)	5'-3' GATGGAGAAAGCCATAGCGA 5'-3' TTGTGCTTGGACGAGAACTG	55ºC
STAT5b + (SEQ ID NO:11) STAT5b – (SEQ ID NO:12)	5'-3' GGGACTCAATAGATCTTGATAATCC 5'-3' AACTGAGCTTGGATCCGCAGGCTCT	65ºC
Actin + (SEQ ID NO:13) Actin – (SEQ ID NO:14)	5'-3' CAATTCCATCATGAAGTGTGAC 5'-3' ATCTTGATCTTCATGGTGCT	65ºC

Please replace paragraph **[0226]** of the published application with the following rewritten paragraph:

[0226] At least 500,000 events per sample were acquired with a BD FACS Calibur (BD Bioscience, Palo Alto, Calif.). Data analysis used Cell Quest and Cell Quest Pro software (BD Bioscience, Palo Alto, Calif.). Matched isotype controls for all antibodies were used to detect

background fluorescence (supplied by Caltag and BD Bioscience, Palo Alto, Calif.). All human antibodies were pre-tested on naïve-untransplanted mice to test for any cross-reactivity. To detect human-originated cells, BM DNA was extracted (QIAprep Spin Miniprep Kit, Qiagen) according to manufacturer instructions. DNA samples (100ng, 2μl) were incubated in 10μl containing 1μl Light Cycler™ DNA master hybridization probe (Roche Molecular Biochemicals). 1μl primers (5μM sense and 5μM antisense), 1μl probes, (5μM anchor and 5μM sensor), 1.2μl $MgCl_2$ (3mM) and nuclease-free water. TNFα primer and probe sequences are listed below in Table 2 (SEQ ID NOS:15-20). PCR involved 45 cycles (95°C. for 10 sec, 65°C. for 7 sec, and 72°C. for 20 sec). Standard curves were generated by mixing mononuclear cells (MNCs) from human CB together with mouse BM, total number of cells being $5x10^6$ per concentration with mixtures of 0, 0.5, 1, 2, 5, 10, 20, 40, 60, 80 and 100% human cells. The human probe and primer were found negative in naïve mice.

Please replace Table 2 as originally filed with the following replacement Table 2:

Table 2: DNA sequence of primers and probes for TNFα

Name	5'-3' sequence	Sequence Name
Human sense	AGGAACAGCACAGGCCTTAGTG	SEQ ID NO:15
Human antisense	AAGACCCCTTCCAGATAGATGG	SEQ ID NO:16
Human probe	GCCCCTCCACCCATGTGCTCC-FL AC-RED640	SEQ ID NO:17
	CACCCACCACCATCAGCCGCATC	SEQ ID NO:18
Mouse sense	GGCTTTCCGAATTCACTGGAC	SEQ ID NO:19
Mouse antisense	CCCCGGCCTTCCAAATAAA	SEQ ID NO:20

FL- sensor, AC- anchor

* Nucleotide sequences are based on human and mouse TNFα genes (GenBank Accession Numbers M26331 and Y00467, respectively) [Nitsche A. *et al.* (2001) *Haematologica* 86:693-699].